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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

TXR NO.: 0053467

DATE: June 14, 2005

SUBJECT: BAS 800 H: Report of the Dose Adequacy Review Team - Concurrence with Dose Selection for a Mouse Carcinogenicity Study
[This memo supercedes the 4/20/05 DART memo, TXR No. 0053315.]

PC Code: 118203; DP Barcode: D316199

FROM: Jessica Kidwell, Executive Secretary
Dose Adequacy Review Team
Health Effects Division (7509C)

THROUGH: Jess Rowland, Chair
Dose Adequacy Review Team
Health Effects Division (7509C)

TO: Joanne Miller, Product Manager
Tracy White, Reviewer
Herbicide Branch, Registration Division (7505C)

This memo is the DART's official acknowledgment of concurrence with the dose level selection for a carcinogenicity study in the mouse for BAS 800 H. The dose levels proposed for this study are as follows:

Males:	0, 1, 5, 25, 75 ppm
Females:	0, 5, 25, 75, 150 ppm

Attached please find the DART's final report and the Registrant's Memorandum of Understanding.

Note to Registrant: Please reference this DART memo in the final study as justification for the dose levels selected.

JUN 20 2005

BAS 800 H REPORT OF THE DOSE ADEQUACY REVIEW TEAM (DART) FINAL

DART Members in Attendance at April 27, 2005 Meeting: (Signature indicates concurrence with the report unless otherwise stated):

William Burnam

Marion Copley

Jessica Kidwell (Executive Secretary)

Jess Rowland

Yung Yang

Attendees from RD: Joanne Miller
Attendees from BASF: Jim Sherman, Wolfgang Kaufmann, Chuck Hastings, Craig Kleppe

The DART met with BASF on April 27, 2005 to discuss dose selection for a mouse carcinogenicity study with BAS 800 H. The DART's recommended dose levels for male (100, 50, 25, 5 ppm) and female (150, 75, 25, 5 ppm) mice were originally presented in an April 20, 2005 memo (TXR No. 0053315) and were slightly different from the BASF-proposed doses. Subsequently, BASF requested a meeting with the DART to further discuss dose selection, specifically for the males. BASF accepted the DART's proposed doses for the female mice.

Recommended doses:

Males: 75, 25, 5, 1 ppm

Rationale: In the 90-day study, severe toxicity in males at 450 ppm manifested as anemia (15% decrease in hemoglobin; 13% decrease in hematocrit), marked elevation of liver enzymes (ALT 793% of control), increased liver weight (134% of control) and liver histopathology (severe/massive diffuse fatty change in the liver, incidence 100%; and lymphoid cell infiltrates, incidence 100%). At the next lower dose of 150 ppm, toxicity was evidenced by anemia (14% decrease in hemoglobin and 11% decrease in hematocrit), elevation of liver enzymes (ALT 292% of control), and liver histopathology (moderate/severe diffuse fatty change in liver, incidence 80%; and lymphoid cell infiltrates, incidence 100%). As pointed out in a detailed review of the pathology data by Dr Kaufmann, BASF, in the April 27, 2005 meeting, the progressive pathological effects observed in the 28- and 90-day studies (i.e, fatty changes and lymphoid infiltration in the liver) at ≥150 ppm were quite severe and that the 150 ppm dose in the 90-day study with male mice was excessive. These pathological changes also had a high likelihood of progressing to necrosis.

Therefore, a dose of 150 ppm was considered too high for the top dose of the carcinogenicity study since the mice may not tolerate it for 18 months. Both the DART and BASF agreed that 75 ppm (which is ½ the excessive dose of 150 ppm) should be selected as the high dose for males in the carcinogenicity study. The DART also agreed with BASF's selection of the lower doses of 25, 5, and 1 ppm.

Females: 150, 75, 25, 5 ppm

Rationale from 4/20/05 DART memo (TXR No. 0053315): In the 90-day study,1350 ppm is excessive based on anemia (14% decrease in hemoglobin; 11% decrease in hematocrit), increased liver weight, and histopathological effects in the liver (lymphoid infiltration, 100% incidence) and moderate/severe centrilobular fatty change, 100% incidence). At the next lower dose of 450 ppm, toxicity was evidenced by anemia (4% decrease in hemoglobin; 5% decrease in hematocrit), increased liver weight, and liver histopathology (lymphoid infiltration, 100% incidence; moderate centrilobular fatty change, 80% incidence). Anemia (5% decrease in hemoglobin and hematocrit) and liver histopathology (moderate centrilobular fatty change, 10%

incidence) was seen at 150 ppm. The NOAEL was 50 ppm.

The DART recommends a top dose of 150 ppm since no toxicity was seen in the 28-day study and the toxicity in the 90-day study was judged to be adverse but not severe and is consistent with the mode of action of this chemical. The DART believes that this top dose of 150 ppm should be adequate to assess the carcinogenicity of the compound. If the top dose of 150 ppm (which is higher than the Registrant's proposed dose of 100 ppm) proves to be excessive, the study should be acceptable because the next lower dose of 75 ppm is one-half of the top dose. The DART agreed with BASF's selection of the lower doses of 25 and 5 ppm.

Note to Registrant for this submission and all future DART submissions: Please submit absolute numbers (including standard deviations) as well as percentages for all data, including body weight, body weight gain, clinical chemistry, and hematology.

BASF Corporation

BASF

May 2, 2005

U.S. Environmental Protection Agency
Office of Pesticide Programs (7505C)
1801 South Bell Street
Arlington, VA 22202 U.S.A.
Attention: Ms. Joanne I. Miller, PM-23

RE: Memorandum of Understanding
BASF - EPA's DART Committee meeting on April 27, 2005

Dear Ms. Miller:

With this letter, BASF is submitting a memorandum of understanding to summarize the BASF and DART committee meeting held on April 27, 2005. The meeting was held to discuss dose selection relevant to a chronic mouse feeding study with BAS 800 H.

Please provide this letter to Ms. Jessica Kidwell, Executive Secretary - DART committee, for approval and further procedural actions by the DART committee.

Please consider the following as conclusions and minutes from the meeting.

- **April 27, 2005**; 3-4 pm Room 325 CM-2
- **Attendance from EPA:** Joanne Miller, Jess Rowland, Marion Copley, Yung Yang, Bill Burnam, Jessica Kidwell
- **Attendance from BASF:** Jim Sherman, Wolfgang Kaufmann, Chuck Hastings, Craig Kleppe

- BASF had originally submitted to DART the dose level proposals for male (75, 25, 5, 1 ppm) and female (100, 50, 25, 5 ppm) mice in the carcinogenesis study with BAS 800 H.
- DART had reviewed the proposal and responded to BASF with recommended doses for male (100, 50, 25, 5 ppm) and female (150, 75, 25, 5 ppm) mice that were slightly different than the BASF-proposed doses.
- BASF requested a meeting with DART to further discuss the dosing levels and to present more detailed information regarding pathology results and data for individual animals. BASF was in general agreement with the DART-proposed doses for the female mice, but concerned that the DART-proposed doses for male mice would exceed the MTD in the carcinogenesis study.
- Dr. Sherman provided an overview of the original dose level proposal submitted by BASF. To clarify issues raised during the original DART review, he also presented additional raw data generated in the 28- and 90-day studies.
- In a detailed review of the pathology data, Dr. Kaufmann demonstrated that the progressive pathological effects observed in the 28- and 90-day studies (i.e., fatty changes and lymphoid infiltration in the liver) at $\geq$150 ppm were indeed quite severe and that the 150 ppm dose in the 90-day study with male mice should be considered as excessive of a MTD. In addition, we discussed the probability that the pathological

26 Davis Drive, Research Triangle Park, North Carolina 27709-3528 telephone (919) 547-2000

changes observed in the 28- and 90-day studies had a high likelihood progressing to necrosis and of being observed at lower doses in the 18-month study.

- Both BASF and DART agreed that it was appropriate to select the high dose for the carcinogenicity study as ½ of the dose that clearly exceeded the MTD (i.e., 150 ppm) in the 90-day study. To better ensure a full characterization of the dose-response curve, BASF also proposed four dose groups for the carcinogenesis study. Considering the above, the doses agreed for the male mice in the carcinogenicity study with BAS 800 H are 75, 25, 5 and 1 ppm.

- Both BASF and DART agreed that the DART proposed doses for female mice were the most appropriate. As such, the doses for the female mice in the carcinogenicity study with BAS 800 H will be 150, 75, 25 and 5 ppm.

Please also find attached a photocopy of the meeting sign-up sheet for EPA records. BASF will hold the original.

Thank you for your assistance with **BAS 800 H**. If you have any questions or concerns, please feel free to contact me directly at 919-547-2615 or via email at *kleppec@basf-corp.com*.

Regards,

Craig D. Kleppe, Ph.D.
Registration Scientist
Tel 919-547-2615
Fax 919-547-2850

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